

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

TRIALALLATE

Chemical Code # 49, Tolerance # 314

March 4, 1999

I. DATA GAP STATUS

Combined, hamster:	No data gap; No adverse effect
Chronic toxicity, dog:	No data gap; No adverse effect
Oncogenicity, mouse:	No data gap; Possible adverse effect
Reproduction, rat:	No data gap; No adverse effect
Teratology, rat:	No data gap; No adverse effect
Teratology, rabbit:	No data gap; No adverse effect
Reverse gene mutation:	No data gap; Possible adverse effect
Forward gene mutation:	No data gap; No adverse effect
<i>In vivo</i> cytogenetic:	No data gap; No adverse effect
Other chromosome effects:	No data gap; Possible adverse effect
Neurotoxicity:	No data gap; Possible adverse effect

Toxicology one-liners are attached.

All record numbers through 164928 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T170539

1 June 2/1/00

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, HAMSTER

314-018, -019 019844 835 "Lifetime Chronic/Oncogenicity Study of Triallate Technical Administered Orally to Syrian Golden Hamsters" by R.A. Adams, Bio-Research Consultants, Inc., Cambridge, MA (contract #C-253 (BR-81-245); 3/6/85). Triallate (lot #LBTT-08-094; purity, 95.4%) was admixed w/rodent diet and fed *ad libitum* to Syrian hamsters (strain B10 F₁D Alexander) for 22 months (males) or 18 months (female hamsters have a shorter lifespan) at 0, 50, 300 or 2000 ppm (120/sex/control group, 70/sex/treated groups). Interim sacrifices of 10/sex/dose (17/sex for controls) occurred at 12 months. Standard parameters were assessed. Test article was stable, homogeneously distributed and within $\pm 6\%$ of target values (incorrect dosing at the LD during weeks 8 & 9 probably did not affect the outcomes). Male mortality was slightly higher during the 1st 65 wks at the MD & HD (10 dead at both doses vs. 5 & 2 in controls & LD), but was unaffected thereafter. A sparing effect may have been present at the HD in females (# dead at ascending doses at 69 wks was 29, 20, 23, 3, and at 79 wks was 70, 67, 55, 32). Body weights at the MD & HD were consistently suppressed in males soon after the start of dosing. A treatment effect on female weights was hard to discern, though, unlike control & LD animals, HD & MD animals did not lose weight pre-termination. Food consumption was depressed in all dosed males mainly during the 1st quarter. Recovery of food consumption combined with lowered body weights was evidence for impaired food efficiency in HD & MD males. Lowered female food consumption was reportedly sporadic (data not shown) and possibly not treatment related. Treated male water consumption was depressed during the 1st 26-39 wks. Flaking/scaly skin appeared to rise in males at the MD & HD. At 12 months total WBC counts in HD males was statistically suppressed & RBC corpuscular volume in HD females was statistically elevated. Terminal hematology revealed no statistically significant effects, but a possible dose-related suppression of hemoglobin, hematocrit & RBC counts (both sexes) suggesting anemia and of HD female WBC counts. Statistically significant excursions in several serum chemistry parameters were more prevalent at 6 & 12 months than at termination. The most consistent effect was a suppression of triglycerides in both sexes at 6 & 12 months and in males only at termination, with effects noted at as low as the MD. Statistically significant suppressions of absolute spleen (F) & heart (M) weights were noted in interim HD animals, and of relative spleen weights (M) at termination. Elevations of relative brain (M) & liver (M/F) weights occurred in interim HD animals. Interim gross necropsies yielded evidence at the HD (and occasionally at the MD) of splotchy/mottled liver (M/F), splenic hypertrophy (M/F), flaking or scaly skin (M/F), & skin melanocyte accumulations (M). Terminal necropsies revealed liver pallor & nutmeg (M), kidney granular/rough surface (M/F) & skin melanocyte accumulations (M). There was no clear effect of test article on the incidence of non-neoplastic or neoplastic histopathologic lesions (combined female adrenal adenomas + carcinomas, 5/120, 4/70, 3/70, 7/70 was of questionable significance). **No adverse effects. NOEL (M) = 50 ppm (weight decrements). NOEL (F) = 300 ppm (hematologic and gross & microscopic changes). **Acceptable.** (Rubin,

clinical chemistry & urinalysis determinations were made at 3, 6, & 12 months. Necropsies & histopathology (on a range of tissues) were conducted on all animals. There were no deaths or treatment-related clinical signs, effects on body weight, food consumption or ophthalmology. Male RBC, hemoglobin & hematocrit levels were somewhat depressed at the HD after 3 months, at the LD & HD (but not the MD) after 6 months, and at the HD (RBC only) after 12 months. These parameters were similarly depressed in HD females after 3 months, but not thereafter. These & other statistically altered hematologic changes were considered equivocal and probably not related to treatment. HD males & females also sustained 77-166% increases in alkaline phosphatase at all time points. Non-statistically significant increases in kidney & liver weights in MD females and HD animals of both sexes were reported. Several macro or micropathologic abnormalities showed higher incidence rates at higher doses, though a treatment relation was uncertain. **No adverse effects**; NOEL (M/F) = 2.5 mg/kg/day (increased alkaline phosphatase). **Acceptable.** (Rubin, 6/4/97)

ONCOGENICITY, MOUSE

**** 314-009, 052, 053; 010805, 159533, 159535-6;** "Two Year Study of Triallate Administered in Feed to Mice" by L.D. Stout, Environmental Health Laboratory, Monsanto Co., St. Louis, MO (report (MSL-3196; 9/27/83). Triallate (lot #GAC-1-14, LUTT 01-014; purity, 94.7%) was admixed w/rodent diet and fed *ad libitum* to B6C3F1 mice for 2 years at doses of 0, 20, 60 & 250 ppm (65/sex/dose). Average daily doses were 3.5-4.9, 10.5-15.1 & 44.0-59.5 mg/kg (males) & 4.9-8.0, 14.7-24.4 & 62.7-99.5 mg/kg (females). Interim sacrifices of 10/sex/dose occurred at 12 months. Survivors were sacrificed at 24 months. Standard observations & parameters were assessed. Test article was stable, homogeneously distributed and w/i 30% of target values (>½ of the values were w/i 10% of target). Longevity appeared unaffected by test article exposure. Mean body weights & food consumption were greater than controls at all doses, though this effect was not considered toxicologically significant. Incidence of alopecia & head tilt/circling movement were distributed "haphazardly" through the doses, thus not considered test article-related (note, however, that the data tables were not included in the Report). Red blood cell parameters were depressed in female interim sacrifices at all doses, though these differences were gone by 24 months. HD males showed depressed reticulocytes at 24 months. MD & HD interim males had statistically elevated glucose (LD males were also somewhat elevated). BUN was statistically depressed in MD interim males (not significant at the HD). Terminal females showed statistically depressed BUN & LDH at the MD & HD, SGPT at the HD, and elevated alk. phos. at the HD. Urinalysis did not reveal abnormalities (data are not presented). Terminal absolute male heart & liver weights were statistically elevated. Changes in relative weights were also noted for several organs, but no clear pattern was established. Gross necropsies revealed a tendency toward liver growths (M: 22/65, 29/65, 26/65, 32/65; F: 6/63, 12/64, 13/65, 14/65), lung discoloration in females (0/63, 1/64, 0/65, 3/65), endometrial polyps (0/63, 0/64, 0/65, 2/65) and uterine cysts (0/63, 0/64, 0/65, 2/65). Histopathology revealed the following increases (asterisks indicate statistical significance, $p < 0.01$; all deaths reported except where indicated): hepatocellular carcinoma in both sexes, terminal sacrifice (**possible adverse effect**) (M: 12/49, 9/47, 6/46, 22/43*; F: 1/37, 3/42, 6/43, 5/40), altered liver focus in both sexes (M: 5/64, 8/65, 7/65, 16/64*; F: 4/62, 4/64, 5/64, 8/65), liver hemangiosarcoma in males (0/64,

MO (study #820123; 7/11/84). Triallate (lot #s LCTT-09-072 & LUTT-06-035; purity, 95.65% & 94.87%, respectively) was administered *via* the diet to 25/sex/dose in each of the F0 & F1 parental generations. Doses: 0, 50, 150, 600 ppm. F0 parentals were treated for 10 wks before mating to produce F1a & F1b offspring. F1a parentals were treated for 11 wks before mating to produce F2a & F2b offspring. Second matings for the F0 & F1 parentals occurred 10 days after weaning. Treatment of adults was continued until sacrifice. Mortality was checked 2x/day, clinical observations, adult body wts. & food consumption were determined weekly and pup wts. were measured until lactation day (LD) 21. Litters were culled to 4/sex on LD 4. Except for F1a pups designated to be parentals, pups were sacrificed on LD 21. Necropsy & histopathology were performed as required by guidelines. Test article was stable, homogeneously distributed & w/ 20% of target values in the diet. Mortality, F0 adults: 4 females (1 control, 1 LD & 2 HD dams); F1 adults: 1 control male, 2 HD females. Necropsies on decedents did not reveal a clear test article-related cause of death. Clinical observations revealed head bobbing movements in 6 F0 HD females & 4 F1a HD females and circling movement in 3 F0 HD females & 6 F1a HD females. Body weights were suppressed by statistically significant margins in both sexes at the HD in the F0 & F1 generations and at the MD in F1 males. No consistent effect on food consumption could be discerned. Mating & fertility parameters were similar among all groups except for a statistically significant reduction in pregnancy rate for the F2b generation (pregnancy rate in females w/copulation plugs, at ascending doses: 100%, 95.8%, 88%, 73.9%; *p<.01). Mean gestational length was reduced for F2b animals (22.2, 22.2, 22.1, 21.7 * days; *p<.01), though the biological significance of this is unclear. There was no clear treatment effect on ability to deliver viable litters. Survival between days 0-4 was statistically reduced for HD F2b pups (97%, 99.7%, 98.8%, 94.5%; *p<.05), with 7 affected litters at the HD vs. 3 in controls. Pup weights were statistically suppressed for the following HD groups: F2b (day 0), F1a, F2a & F2b (day 14), all generations (day 21).Suppressions were also noted for F1a at the MD (days 0, 4, 7, 14 & 21). This effect at day 0 is postulated to be due to the larger litter size. Elevated absolute & relative kidney weights were noted for HD F1 males (several tissues exhibited statistical increases in relative weight, but these were not accorded biological significance). Gross necropsy of adults & weanlings did not reveal abnormalities. Histopathology revealed elevated chronic nephritis in F1 males (9/14, 15/25, 13/25, 15/15) and, possibly, females (3/15 & 6/15, only controls & HD tested) and renal hydronephrosis in F1 females (0/15 & 3/15). **No adverse effects.** Reproductive NOEL = 150 ppm (reduced pregnancy rate [F2, 2nd mating]). Pup NOEL = 50 ppm (weight suppression [F1a]). **Acceptable.** (Rubin, 7/24/97; updated from Remsen, 3/27/85)

TERATOLOGY, RAT

** 314-005, 068; 001197, 164927; 833 "Triallate - A Teratology Study in the Rat" by L. Alvarez, Environmental Health Laboratory, Monsanto Co., St. Louis, MO (report #MSL-2250; 5/10/82). Mated females (25/dose, copulation confirmed by presence of a plug) were subjected to daily gavage doses of Triallate Technical (lot #GAC-I-14, LU-TT-01-014; purity, 95.1%) between gestation days (GD) 6-20 inclusive. The doses were 0 (vehicle control: 8 ml corn oil/kg), 10, 30 or 90 mg/kg. Clinical observations were conducted twice daily during the dosing period. Maternal body weights were determined on GD 0, 6, 10, 14, 18 & 21. Survivors were sacrificed

significant reduction was also noted at the LD during GD 10-14. Except for the decedent, gross necropsy did not indicate clearly test article-related changes. There was no apparent effect of test article on mean numbers of live or dead fetuses, resorptions, implantations ("nidations") or corpora lutea. Mean HD live fetal weights were significantly reduced (mean live weights in grams were 5.2, 5.1, 5.2 & 4.5*; *p<0.01). Malformations at increased incidence at the HD included protruding tongue (0/303, 0/331, 0/306, 2/324; these were not verified by subsequent examination), fused sternebrae (0/153, 0/166, 0/152, 2/161; both were in the same litter) and sternebra severely malaligned (0/153, 0/166, 0/152, 1/161). The relation of these observations to test article exposure is unclear. Variations at increased incidence at the HD included reduced ossification of the skull (0/153, 0/166, 1/152, 35/161; litter values: 0/23, 0/24, 1/23, 15/22*; *p<0.05), malaligned sternebra (0/153, 0/166, 1/152, 13/161; litter values: 0/23, 0/24, 1/23, 7/22*; *p<0.05) and sternebra "unco-ossified" (0/153, 0/166, 1/152, 4/161). **No adverse effects.** Maternal NOEL = 30 mg/kg (weight gain & food consumption decrements). Developmental NOEL = 30 mg/kg (reduced fetal weight, skeletal variations). **Acceptable** (revised from Gee, 3/26/85, Rubin, 7/9/97; upgraded with submission of a retro-spective analysis of the dosing suspensions of Triallate in corn oil to verify the administered dosages; Leung, 2/16/99).

TERATOLOGY, RABBIT

** 314-005, 068; 001195, 164927; 833 "Teratology Study in Rabbits [Triallate Technical]" by K.A. Laughlin, International Research and Development Corp., Mattawan, MI (study #401-146; 1/21/82). Pregnant females (16/dose) were subjected to daily gavage doses between gestation days (GD) 6-28 inclusive. The doses were 0 (vehicle control: corn oil, 0.5 ml/kg), 5, 15 & 45 mg/kg/day. Observations for toxicity were made daily, GD 6-29. Body weights were determined on GD 0, 6, 12, 18, 24 & 29. Survivors were sacrificed on GD 29 after which the uteri were excised and weighed, and the number of viable & nonviable fetuses, early & late resorptions, total implants and corpora lutea were recorded. Gross necropsies were performed on the maternal thoracic & abdominal cavities. Fetuses were weighed, sexed, and examined for external, visceral & skeletal abnormalities. Except for one 5 mg/kg doe that died on GD 16 (fibrinous pleuropneumonia, unlikely to be treatment-related), there were no maternal deaths. Pregnancy rate: 14/16, 15/16, 16/16, 13/16. Abortion rate: 2/16, 0/16, 1/16, 3/16. Two of the 3 aborting does at the HD had congested or consolidated lungs. A moderate increase in HD does w/soft stool and/or stool beneath the cage was noted primarily on GD 25-29. Also noted at the HD, though as single instances, were gelatinous matter in the cage pan, cloudy red eye, and a subcutaneous mass on the neck. Gross necropsies on the does did not reveal clearly test article-related abnormalities, though it should be noted that these data were not presented in detail. HD does gained significantly less weight over the treatment period than controls (weight change in grams over GD 6-29: 322, 360, 350, 22*; *p<0.05). During the GD 18-24 and 24-29 periods HD does actually lost weight. There was no apparent effect on mean numbers of viable fetuses (at ascending doses: 5.4, 5.5, 5.2, 5.9), postimplantation loss (0.9, 0.6, 1.5, 1.1), % postimplantation loss (14.5, 10.0, 22.8, 15.7), total implants (6.3, 6.2, 6.7, 7.0), corpora lutea (8.8, 8.5, 8.4, 8.2) or sex ratio (% males: 46.2, 45.8, 61.5, 47.5). Mean fetal body weight was significantly reduced at the HD (mean fetal weights in grams: 42.5, 40.4, 38.4, 32.9*; *p<0.01). Fetal exams revealed the

suspensions to verify the dosages administered, Leung, 2/16/99).

REVERSE GENE MUTATION

****314-011 010811 842** "Mutagenicity Evaluation of Triallate, Lot XHI-50, Using *Salmonella* and *Saccharomyces* Indicator Organisms" by D.J. Brusick, Dept. of Molecular Toxicology, Litton Bionetics, Inc., Kensington, MD (project #LBI 2683; 7/77). -10⁸ cells from overnight cultures of the tester strains (*Salmonella typhimurium*, tester strains TA-98, -100, -1535, -1537 & -1538 and *Saccharomyces cerevisiae*, tester strain D4) were added to histidine-deficient media +/- Aroclor-activated S9 microsomes at Triallate (lot #XHI-50; an amber liquid; purity, 97.3%) concentrations of 0 (DMSO solvent control), .001, .1, 1 or 5 F/plate (10 F/plate was run in the repeat assay on TA-1535 and in the original assay +S9 for TA-100; thus the Triallate concentrations were approximately equal to a range of 0-10 Fg/plate) and incubated for 48 hr at 37°C. The number of histidine-independent colonies was scored on each plate. Single plates were run for each concentration. A repeat assay was conducted on tester strain TA-1535 at those concentrations where positive results were obtained in the first test. Appropriate positive controls were run for each tester strain and activation condition. A positive response was present for strains TA-1535 and TA-100 with and without activation and for strain TA 98 with activation. Thus Triallate exhibits a **positive genotoxic effect** in those tester strains. **Acceptable.** (Rubin, 8/14/97; updated from Remsen, 3/27/85)

FORWARD GENE MUTATION

314-011 010809 842 "Mutagenicity Evaluation of XHI-50 in the Mouse Lymphoma Assay" by D.J. Brusick, Dept. of Molecular Toxicology, Litton Bionetics, Inc., Kensington, MD (project #LBI 2684; 8/77). An undesignated number of L5178Y cells heterozygous for thymidine kinase (*i.e.*, TK +/-) and thus sensitive to bromodeoxyuridine were exposed as single dishes to Triallate (lot #XHI-50; an amber liquid; purity, 93.7%) at doses of 0 (both a negative control and a solvent control containing DMSO), .005, .01, .02 & .04 F/ml (dose range was determined by a preliminary cytotoxicity experiment for which data were not provided) +/- S9 activating microsomes for 4 hours. Following exposure the cells were washed, fed and subcultured 3 times over 3 days to allow mutant expression and plated in agar in the presence of an undesignated amount of the selective agent bromodeoxyuridine to determine the number of mutant colonies, and in the absence of BrdU to determine the number of viable cells. Positive controls were 0.5 F/ml ethylmethanesulfonate (-S9) and 0.3 F/ml dimethylnitrosamine (+S9). Cytotoxicity was evident at the HD both in the presence & absence of S9 and at the MHD in the presence of S9 by the inhibition of suspension growth during the mutant expression period. Despite the success of the positive controls, Triallate did not increase the mutant frequency at the concentrations tested. **Unacceptable** (insufficient experimental details, no duplication of test cultures, no repeat experiment). (Rubin, 8/15/97; updated from Remsen, 3/28/85)

****314-043; 75528; *In Vitro* Gene Mutation Assay (HGPRT Locus) in Cultured Chinese**

from Syrian Golden Hamster” by W.F. Blazak, Environmental Health Laboratory, Monsanto Co., St. Louis, MO (study #SI-80-478/ML-80-142; 2/82). Hamsters were exposed to Triallate (lot #LUTT-04-58, GAC-I-15; purity not stated) *via* the diet at 0, 600, 2000 or 6000 ppm for 6/7 or 13/14 weeks. There were 5 animals/sex/dose for 0, 600 & 2000 ppm at both sacrifice times and 7/sex for 6000 ppm at both sacrifice times. Positive controls received a single intraperitoneal injection of triethylenemelamine (TEM; 1 mg/kg) 24 hr before sacrifice. Approximately 2 hr before sacrifice the animals were injected with 2 mg of colchicine to induce metaphase arrest. (The doses of TEM & colchicine were established in a preliminary experiment.) Following sacrifice bone marrow cells from each femur were extracted, fixed, put onto microscope slides and stained. 1000 cells per animal were scored for mitotic index (the percentage of nucleated cells in metaphase) and at least 60 cells/animal for chromosomal aberrations (animals with fewer than 30 analyzable cells were excluded from calculation of group statistics). 4 cytogeneticists independently analyzed half of each exposure group (*i.e.*, 2/half). 2 observations suggest that the HD was sufficient to induce toxicity: 1. Mortality during the feeding phase of the 13/14-week animals resulted in only 5 HD males being available for analysis, and 2. Of the 9 non-positive control hamsters with insufficient cells for chromosome analysis (presumably due to toxicity), 7 were at the high dose. 6/7 week sacrifice: While there was a slight decrease in mitotic index (at increasing doses MI [per 1000 cells] = 5.91, 6.43, 6.62, 4.01), this did not attain statistical significance. There was no significant effect either on the mean chromosomal aberration frequency per cell per animal or on the mean aberrant cell frequency per animal. 13/14 week sacrifice: MI appeared unaffected by treatment. As in the 6/7 week sacrifice, there was no discernible effect on chromosome aberrations. The positive control, TEM, was very successful in inducing aberrations at both sacrifice times. Triallate appears not to induce chromosome aberrations under the conditions tested. **Acceptable**. (Rubin, 8/1/97; upgraded from unacceptable [Shimer, 4/5/90])

OTHER CHROMOSOMAL EFFECTS

****314-043; 75529**; “*In Vitro* Sister Chromatid Exchange Assay in Chinese Hamster Ovary Cells Treated with Triallate Technical”; Bioassay Systems Corp., Woburn, MA; 9/82; triallate (lot#s-LUTT-01-014 (GAC-I-14):95.1%; LBTT-11-126:96.5); non-activated-80, 64, 56, 48, 32, 16 or 0 FM (solvent (DMSO-0.2%) and media controls) w/o S9 (Mitomycin C positive control) 30 hr exposure; at 403, 322, 242, 161, or 81 for 2 hour exposure; activated-40, 32, 24, 20, 16, 8, 4 or 0 (solvent (DMSO-0.2%) and media controls) with S9 (cyclophosphamide positive control) 4 hour exposure; at 81, 64, 48, 32, or 16 for 2 hour exposure, in Chinese Hamster ovary (CHO) cells; toxicity based on reduced mitotic index: $MI \leq 0.017$ at 80 FM (non activated) 30 hour exposure; $MI \leq 0.036$ at 80 FM (activated) 4 hour exposure; **ADVERSE EFFECT**- dose-response increase in frequency of SCEs (non activated), increase in SCEs due to treatment, but less consistent dose-response (activated). **Acceptable**. (Moore, 10/18/90)

NEUROTOXICITY

314-007 020477 817 “Effect of a Single Oral Dose of Triallate on Hens” by M.B. Abou-Donia, Dept. of Pharmacology, Duke University Medical Center, Durham, NC (no study #;

such that by day 20 the only sign was slowness of movement. After the 2nd dose weakness, diarrhea & uncontrolled neck movement were evident, developing into a reluctance to walk (evidenced by sitting on their hocks), leg weakness and slow movements. There was improvement with time such that by day 42 only residual leg weakness (evidenced by slipping on the floor when forced to run) was present in 4 hens. 1250 mg/kg: Leg weakness, preference for sitting, slipping on the floor, slowness of movement and involuntary head shaking were evident within one day of treatment. General improvement was manifested with time. A more severe response occurred after the 2nd dose, with the hens showing weakness, inability to stand and involuntary neck movements. Improvement again occurred, with only slight leg weakness evident by 42 days. 625 mg/kg: Within 1 day leg weakness was evident which continued for 7 days followed by recovery. Interestingly, the hens manifested a milder response after the 2nd dose, with recovery evident by day 28. 312.5 mg/kg: Slight leg weakness occurred after both doses. Normality was evident by day 28. 750 mg/ml TOCP: At 7 days ataxia developed, progressing to paralysis by 17 days and sacrifice at 21 days. Body weights: Weight loss was apparent at all doses during the 1st week after both treatments with the degree of loss proportional to dose (raw data not presented). Some or all of the lost weight was regained, though HD hens remained 16% below controls by day 42. Histopathology: No lesions were evident in experimental animals. TOCP treatment generated areas of peripheral multifocal demyelination, myelin fragmentation & nerve sheath widening, and axonal degeneration. Spinal cords showed swollen lateral & dorsal tract axons. In conclusion, while Triallate generated neurotoxicity, delayed neurotoxicity was not evident. **Acceptable.** (Rubin, 8/14/97; updated from Berliner, 4/11/85)

Delayed neurotoxicity

314-022 035823 826 "Studies on Subchronic (90 days) Delayed Neurotoxicity of Triallate in Hens" by M.B. Abou-Donia, Laboratory of Neurotoxicology, Dept. of Pharmacology, Duke University, Durham, NC (study #MU-81-266B; 7/9/84). Daily oral doses of Triallate (lot #06-062; purity, 95.72%) were administered daily for 90 consecutive days to 10 young adult Leghorn laying hens/dose at 0 (negative control: empty gelatin capsules), 25, 50, 100, 200 or 300 mg/kg-bw. An additional group of 10 positive control hens received capsules containing 10 mg/kg/day tri-o-cresyl phosphate (TOCP). Observations for behavioral abnormalities, locomotor ataxia & paralysis were made daily both inside the cage and while the animals moved freely outside the cage. Body weights were determined weekly. Histopathology on the spinal cord & brain, and sciatic, tibial & peroneal nerves was performed. All hens in the HD group were killed on day 36 due to poor condition. These hens experienced side-to-side head movement after 2-3 days of dosing, disappearing after 7-8 days. Lethargy & reluctance to walk set in after 14-21 days. The latter signs were considered possibly due to malnutrition evidenced by severe weight loss since no ataxia developed. Their comb became pale with development of these symptoms. At 200 mg/kg one hen died and 3/10 hens showed side-to-side neck movement which disappeared after a week. Reluctance to walk, possibly due to weight loss, was seen during the 1st 4 weeks. The remaining 9 hens at this dose were walking normally at the end of the dosing period. No effects were noted at the lower 3 doses. Hens receiving TOCP "showed various stages of mild to severe ataxia at 30-40 days which progressively increased to severe ataxia to paralysis at termination" (Report p. 6). One of these animals died on day 87. The only histopathologic changes noted in the Triallate-treated animals was minimal or slight axonal swelling and/or

were administered daily either onto the ventral wing surface (alternating when necessary in the case of Triallate with the dorsal thoracic & breast areas to avoid accumulation) or orally in gelatin capsules. For doses over 100 mg/kg, the test article was delivered as the technical material while for lower doses a 20% emulsifiable concentrate in xylene containing 2% Triton X-100 (dermal) or 20% solution in oleic acid (oral) was used. The # of hens/dose appears to have been 3, though this was not explicitly stated. Dosing was discontinued in cases of severe narcosis or ataxia because of prior demonstration that such animals would starve if kept on the regimen. Reported doses were, for Diallate dermal: 40-42, 80-110, 142-160 & 260-280 mg/kg/day, Diallate oral: 17-22, 81-106 & 160-160 mg/kg/day, Triallate dermal: 294-330 mg/kg/day, and Triallate oral: 82-95 & 340-420 mg/kg/day (the latter dose was reported only in the text of the Report). Observations for narcosis were performed daily prior to removal from cages for assessment of severe narcosis & ataxia. Body weights & egg production were monitored in all hens, with feed consumption monitored in some. Known & suspected organophosphate delayed neurotoxicants (leptophos, terbufon, chlorpyrifos, OMS-1297, trichlorfon & DEF) were examined simultaneously in part I, acting as a positive control. Histopathology was not done. Diallate produced an increasingly severe & persistent narcosis at higher doses by both routes of exposure (along with a suppression of egg laying & severe weight loss at doses over 40 mg/kg). Comparative oral vs. dermal Diallate morbidity depended on the cumulative dose. Little effect was noted at oral doses of near 20 mg/kg/day or dermal doses near 40 mg/kg/day, both for 99 days. Triallate induced no signs of ataxia or narcosis at oral doses of 82-95 mg/kg/day or dermal doses of 294-330 mg/kg/day, though the oral dose induced a transient decrease in food consumption & mean eggs/wk. Oral doses between 340-420 mg/kg/day were discontinued after 25 days due to severe weight loss, and the birds were sacrificed on day 36 in poor condition.

Supplemental. (Rubin, 6/10/97)